2-(*trans*-4-amino-cyclohexyl-amino)-9-ethyl-6-(4-trifluoromethyl-phenyl-amino)-9*H*-purine,
6-(3-fluoro-phenyl-amino)-9-ethyl-2-(*trans*-4-hydroxy-cyclohexyl-amino)-9*H*-purine,
6-(3-cyano-phenyl-amino)-9-ethyl-2-(*trans*-4-hydroxy-cyclohexyl-amino)-9*H*-purine,
2-(*cis*-3-amino-cyclohexyl-amino)-6-(3-chloro-phenyl-amino)-9-ethyl-9*H*-purine, and
6-(4-fluoro-phenyl-amino)-2-(2-hydroxy-ethyl-amino)-9-isopropyl-9*H*-purine
or a pharmaceutically acceptable salt of such a compound. --

-- 18. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a therapeutically effective amount of a compound of the formula I according to claim 2, or a pharmaceutically acceptable salt thereof. --

-- 19. A method of treating tumors which are responsive to the inhibition of $p34^{cdc2}$/cyclin $B^{cdc13}$ kinase, comprising administering to a subject in need of such treatment a therapeutically effective amount of a compound of formula I according to claim 2, or a pharmaceutically acceptable salt thereof. --

## REMARKS

A favorable reconsideration of this application is respectfully requested in view of the foregoing amendments and the following remarks.

Acknowledgment is hereby made of a telephone discussion between Examiner Mark Berch and the undersigned on May 11, 2000 regarding the "supplemental" Official Action dated May 2, 2000. Although not explicitly set forth in the "supplemental" Official Action, in the above-mentioned discussion on May 11, 2000, the Examiner confirmed that the due date for responding to "all" of the issues, i.e., the issues contained in the Official Action dated March 29, 2000 and the additional issues set forth in the "supplemental" Official Action dated May 2, 2000 is three months from the latter date, i.e., the due date is August 2, 2000.

By the foregoing amendments to the specification, certain inadvertent errors noted have been corrected. The amendment to line 23 on Page 46 is supported by the disclosure

on Page 32, line 16 and by Examples 26-28; the amending of the identity of the compound of Example 96 on Page 72 is evident from the identity of the starting material, viz., "2-chloro-9-isopropyl-6-(5-fluoro-phenyl-amino)-9H-purine" and the FAB-MS value: $(M+H)^+$ = 331) set forth; and the amending of the partial identity of the starting material on Page 77 is evident from the identity of the resultant compound.

Claims 1-16 were presented for examination, and Claims 2-4, 6 and 14-19 are now present in the case.

Claims 1, 5, 8, 11 and 12 have been cancelled without replacement.

Claim 7 has been cancelled and replaced by "new" Claim 17.

Claims 9 and 10 have been cancelled and replaced by "new" Claim 18.

Claim 13 has been cancelled and replaced by "new" Claim 19.

Claim 2 has been amended to: 1) place it in independent form; 2) explicitly reflect the meaning of the dashed lines in the structural formula, support for which may be found in formulae Ia and Ib on Pages 2 and 3, respectively; 3) delete "or" in the definition of substituents "$R_1$" and "$R_4$", where appropriate, and replace "commas" with "semi-colons" to separate significances in the definition of substituents "$R_1$" and "$R_4$", where appropriate; 4) exclude "hydrogen as a significance and clarify the definition of "Z" in the "acyl" significance regarding the "$R_4$" substituent; 5) replace "thio" with <u>mercapto</u> in the definition of the "$R_4$" substituent; and 6) exclude a "further" significance in the definition of the "$R_5$" substituent.

Claim 3 has been amended so that it now depends on Claim 2.

Claim 4 has been amended to: 1) change its dependency to that of Claim 2; 2) replace "commas" with "semicolons" to separate the first few significances in the definition of "$R_5$", and replace an inadvertent semicolon with a <u>comma</u> before the significance

"benzyl" in the "acyl" significance of "$R_5$"; and 3) exclude "hydrogen" as a significance and clarify the definition of "Z" in the "acyl" significance of "$R_5$" consistent with that in Claim 2.

Claim 6 has been amended to: 1) change its dependency to that of Claim 2; 2) replace commas with semicolons to separate the first few significances in the definition of "$R_1$"; 3) explicitly reflect the meaning of the dashed lines in the structural formula; and 4) delete "hydroxyl" as a substituent of lower alkyl in the definition of "$R_5$", consistent with that in Claim 2.

Claim 14 has been amended to: 1) replace the passage "2-amino-6-anilino-purine derivative" with the word compound on line 1; 2) delete the "full" definitions of the substituents in the structural formula as being redundant in view of the insertion of the passage $R_1$, $R_2$, m, n, $R_3$, $R_4$ and $R_5$ are as defined in Claim 2; and 3) delete certain passages at the end of the description of process a).

In any event, none of the amendments to the claims is seen to raise any question of "new" matter. In this connection, it should be mentioned that the: 1) exclusion of "hydrogen" as a significance in the definition of "Z" in Claims 2 and 4; and 2) exclusion of "hydroxyl-substituted alkyl" as a significance in the definition of "$R_5$" in Claims 2 and 6 is supported by the CCPA decision rendered in In re Driscoll, 195 USPQ 434.

With regard to the Examiner's request that the specification be amended to reflect the fact that this case is a "371" application, the Examiner's attention is respectfully invited to the "Note" at the end of MPEP 1893.03(c) which states, in part:

> "since the international applications is not an earlier application (it has the same filing date as the national stage), a priority claim in the national stage to the international application is inappropriate. Accordingly, it is not necessary

for the applicant to amend the first sentence of the specification to reference the international application for a national stage application filed under 35 U.S.C. 371."

It is clear that the Examiner's request clearly lacks any basis. Accordingly, the Examiner is respectfully requested to reconsider the request and withdraw it.

As to the Examiner's comment that this case lacks an Abstract, enclosed herewith is a copy of Page 94 which contains an Abstract of the invention.

The Examiner has rejected Claims 2 and 4-6 under the first and second paragraphs of 35 USC 112 because the claimed invention is not described in such full, clear and exact terms as to enable any person skilled in the art to make and use the same, and/or failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention. More particularly, it is the Examiner's contention that certain of the significances for the "$R_4$" and "$R_5$" substituents in Claims 2 and 4-6 are broader than their corresponding definitions in Claim 1 and, therefore, the former claims are improperly dependent upon Claim 1. Since Claim 1 has been cancelled without replacement, this rejection is believed to have been mooted.

The Examiner has also rejected Claims 10-13 under the first paragraph of 35 USC 112 as being based on a specification which does not enable one skilled in the art to make and use the invention. More particularly, the Examiner is troubled by the presence of the term "tumors" generally in Claims 10-13 and doubts whether the claimed compounds would be effective against all tumors. First of all, Claims 9 and 10 have been replaced by "new" Claim 18, which claim does not contain the term "tumors". In addition, Claims 11 and 12 have been cancelled as being "non-statutory".

Although Applicants do not agree that "original" Claim 13 is based upon a specification which is "non-enabling", the cancellation of Claim 13 and its replacement with "new" Claim 19 is believed to have overcome this rejection. Thus, it is Applicants' belief

that the instant specification clearly discloses the effectiveness of the instantly claimed compounds in treating tumors which are responsive to the inhibition of $p34^{cdc2}$/cyclin $B^{cdc13}$ kinases. To wit, in the last paragraph on Page 17 of the instant specification, it is indicated that the compounds of formula I and their pharmaceutically acceptable salts inhibit the enzyme $p34^{cdc2}$/cyclin $B^{cdc13}$ kinase, which kinase controls certain phases during cell division. In this connection, the ability of the instantly claimed compounds to inhibit $p34^{cdc2}$/cyclin $B^{cdc13}$ kinase is demonstrated by the pharmacological test method described in the fourth paragraph on Page 18 of the instant specification. Moreover, because of their ability to inhibit $p34^{cdc2}$/cyclin $B^{cdc13}$ kinase, the instantly claimed compounds are believed to be useful in treating tumors, which belief is unequivocally established by the in vitro test method described in the paragraph bridging Pages 18 and 19 of the instant specification, and by the in vivo test method described in the paragraph bridging Pages 19 and 20 of the instant specification. In brief, it is Applicants' belief that the instant specification clearly enables one skilled in the art to practice the invention as claimed in "new" Claim 19 without undue experimentation.

In view of the foregoing, the Examiner is respectfully requested to reconsider the "non-enabling" rejection (as it applies to "new" Claim 19) under the first paragraph of 35 USC 112 and withdraw it.

The Examiner has additionally rejected Claims 1-16 under the second paragraph of 35 USC 112 as being indefinite for various reasons which will be commented on in the order that they appear in the "respective" Office Actions as follows:

1) The amending of Claim 2 to explicit reflect the meaning of the dashed lines in the structural formula is believed to have overcome this portion of the rejection.

2) The insertion of semicolons in Claims 2, 4 and 6, where appropriate, to separate significances is believed to have overcome this portion of the rejection.

3), 4) and 5) The cancellation of Claim 1 and the limitation of the "broad" compound, per se, scope to that of Claim 2 is believed to have overcome these portions of the rejection.

6) The amending of the definition of "Z" in the "acyl" significance regarding the "$R_4$" substituent in Claim 2 and the "$R_5$" substituent in Claim 4 is believed to have overcome this portion of the rejection.

7) The replacement of "thio" with mercapto in the definition of the "$R_4$" substituent in Claim 2 is believed to have overcome this portion of the rejection.

8) The replacement of Claim 7 with "new" Claim 17, which claim is directed to a Markush group of specifically disclosed compounds, is believed to have overcome this portion of the rejection.

9) The cancellation of Claim 8 as being "non-statutory" is believed to have mooted this portion of the rejection.

10) The cancellation of Claims 11 and 12 as being "non-statutory" is believed to have mooted this portion of the rejection.

11) The amending of Claim 14 to delete certain passages at the end of the description of process a) is believed to have overcome this portion of the rejection.

12) The amending of Claims 15 and 16 to place them in independent form is believed to have overcome this portion of the rejection.

In view of the cancellation of Claims 1, 8, 11 and 12, the foregoing amendments to Claims 2, 4, 6 and 14-16, and the presentation of "new" Claims 17 and 19, the Examiner is respectfully requested to reconsider the rejection under the second paragraph of 35 USC 112 and withdraw it.

Turning to the "prior art" rejection, the Examiner has rejected Claims 1, 2 and 5-15 under 35 USC 102(a) as being anticipated by Mackman, et al. (USP 5,866,702). More particularly, it is the Examiner's contention that certain of the specific compounds in Col. 16 of the Mackman, et al. reference anticipates Claims 1, 2 and 5-15. Although Applicants do

not dispute the Examiner's contention, it is respectfully pointed out that since the effective date of the Mackman, et al. reference is subsequent to the filing date of Applicants' earliest Swiss priority application, viz., Swiss Application No. 03094/95, filed November 1, 1995, the benefit of which Applicants are entitled to under 35 USC 119, Mackman, et al. is not an effective reference against any of the instant claims. In this connection, it should be noted that "original" Claims 1-4 and 6-16 of the instant application correspond literally to Claims 1-15 of Swiss Application No. 03094/95, respectively, save for the fact that whereas Claim 5 of the latter covers all salts of the compounds, "original" Claim 6 of the instant application is limited to "pharmaceutically acceptable salts", exclusively. In any event, although acknowledging that the earliest Swiss priority document antedates the Mackman, et al. reference, the Examiner indicates that said priority document cannot be relied upon to overcome this rejection because it is in a non-English language and a certified English translation has not been submitted. However, enclosed herewith is a certified English translation of Swiss Application No. 03094/95 which, in effect, "perfects" Applicants' "claim of priority". Accordingly, the 35 USC 102(a) rejection of certain of the instant claims as being anticipated by Mackman, et al. is believed to have been overcome.

The Examiner has also rejected Claims 3 and 4 under 35 USC 103(a) as being unpatentable over Mackman, et al. (as identified above). More particularly, it is the Examiner's contention that the specific compound on line 33 in Col. 16 of the Mackman, et al. reference coupled with certain other teachings therein render certain of the compounds in Claims 3 and 4 prima facie obvious. In this connection, although acknowledging certain differences between the specific compound in the Mackman, et al. reference and the closest structurally similar compounds embraced by Claims 3 and 4, it is the Examiner's belief that said compound coupled with certain other teachings in the Mackman, et al. reference would have motivated one skilled in the art to arrive at certain of the compounds embraced by Claims 3 and 4 and, in support thereof, relies on a myriad of case law. As indicated in the previous rejection, since the effective date of the Mackman, et al. reference is subsequent to the filing date of Swiss Application No. 03094/95, the benefit of which Applicants are entitled to under 35 USC 119, Mackman, et al. is not an effective reference against any of the instant claims. Accordingly, the 35 USC 103(a) rejection of Claims 3 and

4 as being prima facie obvious over Mackman, et al. is believed to be overcome by the enclosed certified English translation of Applicants' earliest Swiss priority application.

Applicants acknowledge the Burns, et al. reference (USP 5,663,154) cited by the Examiner but not applied in rejecting any of the claims. However, no further comment concerning this reference is believed necessary.

All of the rejections of record having been overcome, the instant application is deemed to be in condition for allowance, and an early notice to that effect is earnestly solicited.

Although three "new" claims were added by this Amendment, nine claims were cancelled. In any event, since neither the total number of claims nor the total number of independent claims now present in the case exceeds the highest total previously paid for, no additional fee is necessitated by the added claims.

Respectfully submitted,

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Encls.: Copy of Abstract Page 94
Certified English translation of
Swiss Priority Application No. 03094/95
Postcard

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